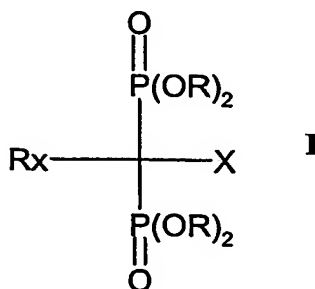


CLAIMS

- 1.) A pharmaceutical preparation which comprises in combination a bisphosphonate of formula I, or a physiologically acceptable and -cleavable ester or a salt thereof



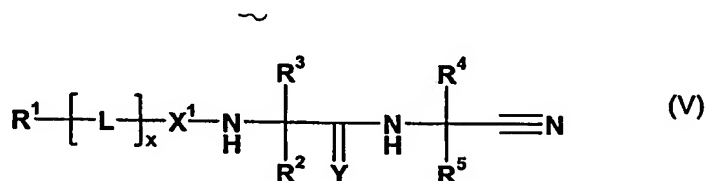
wherein

X is hydrogen, hydroxyl, amino, alkanoyl, or an amino group substituted by C₁-C₄ alkyl, or alkanoyl;

R is hydrogen or C₁-C₄ alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles), or a pharmaceutically acceptable salt thereof or any hydrate thereof; and

- a) a cat K inhibitor of formula V, or a physiologically acceptable and -cleavable ester or a salt thereof



wherein R¹ is optionally substituted (aryl, aryl-lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl or heterocyclyl-lower alkyl);

R² and R³ together represent lower alkylene, optionally interrupted by O, S or NR⁶, so as to form a ring with the carbon atom to which they are attached, and R⁶ is hydrogen, lower alkyl or aryl-lower alkyl;

R^4 and R^5 are independently H, or optionally substituted (lower alkyl or aryl-lower alkyl), -C(O)OR⁷, or -C(O)NR⁷R⁸, wherein R^7 is optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl), and R^8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl); or

R^4 and R^5 together represent lower alkylene, optionally interrupted by O, S or NR⁶, so as to form a ring with the carbon atom to which they are attached, and R^6 is hydrogen, lower alkyl or aryl-lower alkyl; or

R^4 is H or optionally substituted lower alkyl and R^5 is a substituent of formula -X²-(Y¹)_n-(Ar)_p-Q-Z wherein

Y¹ is O, S, SO, SO₂, N(R⁶)SO₂, N-R⁶, SO₂NR⁶, CONR⁶ or NR⁶CO;

N is zero or one;

P is zero or one;

X² is lower alkylene; or when n is zero, X² is also C₂-C₇-alkylene interrupted by O, S, SO, SO₂, NR⁶, SO₂NR⁶, CONR⁶ or NR⁶CO, and R^6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

Z is hydroxyl, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sulfonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y¹-lower alkylene or C₂-C₇-alkylene interrupted by Y¹;

X¹ is -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, or -P(O)(OR⁶)-, and R^6 is as defined above;

Y is oxygen or sulphur;

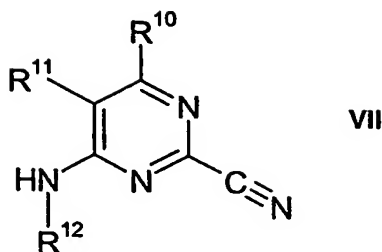
L is optionally substituted -Het-, -Het-CH₂- or -CH₂-Het-, and Het is a hetero atom selected from O, N or S; and

X is zero or one; and

aryl in the above definitions represents carbocyclic or heterocyclic aryl; or alternatively

b) another class of cat K inhibitors of formula VII, or a physiologically acceptable and -cleavable ester or a salt thereof

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wherein

R^{10} is H, $-R^{14}$, $-OR^{14}$ or $NR^{13}R^{14}$,

wherein R^{13} is H, lower alkyl or C_3 to C_{10} cycloalkyl, and

R^{14} is lower alkyl or C_3 to C_{10} cycloalkyl, and

wherein R^{13} and R^{14} are independently, optionally substituted by halo, hydroxy, lower alkoxy, CN, NO_2 , or optionally mono- or di-lower alkyl substituted amino;

R^{11} is $-CO-NR^{15}R^{16}$, $-NH-CO-R^{15}$, $-CH_2-NH-C(O)-R^{15}$, $-CO-R^{15}$, $-S(O)-R^{15}$, $-S(O)_2-R^{15}$, $-CH_2-CO-R^{15}$ or $-CH_2-NR^{15}R^{16}$,

wherein

R^{15} is aryl, aryl-lower alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl,

R^{16} is H, aryl, aryl-lower alkyl, aryl-lower-alkenyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl, or

wherein R^{15} and R^{16} together with the nitrogen atom to which they attached are joined to form an N-heterocyclyl group,

wherein N-heterocyclyl denotes a saturated, partially unsaturated or aromatic nitrogen containing heterocyclic moiety attached via a nitrogen atom thereof having from 3 to 8 ring atoms optionally containing a further 1, 2 or 3 heteroatoms selected from N, NR^{17} , O, S, $S(O)$ or $S(O)_2$ wherein R^{17} is H or optionally substituted (lower alkyl, carboxy, acyl (including both lower alkyl acyl, e.g. formyl, acetyl or propionyl, or aryl acyl, e.g. benzoyl), amido, aryl, $S(O)$ or $S(O)_2$), and wherein the N-heterocyclyl is optionally fused in a bicyclic structure, e.g. with a benzene or pyridine ring, and wherein the N-heterocyclyl is optionally linked in a spiro structure with a 3 to 8 membered cycloalkyl or heterocyclic ring wherein the heterocyclic ring has from 3 to 10 ring members and contains from 1 to 3 heteroatoms selected from N, NR^{16} , O, S, $S(O)$ or $S(O)_2$ wherein R^{16} is as defined above), and

wherein heterocyclyl denotes a ring having from 3 to 10 ring members and containing from 1 to 3 heteroatoms selected from N, NR¹⁷, O, S, S(O) or S(O)₂ wherein R¹⁷ is as defined above), and

wherein R¹⁵ and R¹⁶ are independently, optionally substituted by one or more groups, e.g. 1-3 groups, selected from halo, hydroxy, oxo, lower alkoxy, CN or NO₂, or optionally substituted (optionally mono- or di-lower alkyl substituted amino, lower-alkoxy, aryl, aryl-lower alkyl, N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein the optional substitution comprises from 1 to 3 substituents selected from halo, hydroxy, lower alkoxy, lower alkoxy-lower alkyl, lower alkoxy-carbonyl, CN, NO₂, N-heterocyclyl or N-heterocyclyl-lower alkyl, or optionally mono- or di-lower alkyl substituted amino;

R¹² is independently H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₀cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl), and wherein R² is optionally substituted by halo, hydroxy, oxo, lower alkoxy, CN, NO₂, or optionally mono- or di-lower alkyl substituted amino.

for simultaneous, sequential or separate use.

- 2.) The pharmaceutical preparation according to claim 1; whereas its use is for the treatment of malignant diseases, bone metastasis, cancer cell growth, or/and cancer therapy-induced bone loss.
- 3.) The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a malignant disease, bone metastasis, cancer cell growth or/and cancer therapy-induced bone loss; or a method of treating a patient suffering from a malignant disease, bone metastasis, cancer cell growth, or/and cancer-therapy-induced bone loss comprising administering to the patient an effective amount of a bisphosphonate according to claim 1 and an effective amount of a cathepsin K inhibitor according to claim 1.
- 4.) The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a benign disease, bone loss disease, osteoporosis, osteoarthritis; or

a method of treating a patient suffering from a benign disease, bone loss disease, osteoporosis, osteoarthritis comprising administering to the patient an effective amount of a bisphosphonate according to claim 1 and an effective amount of a cathepsin K inhibitor according to claim 1.

5.) A pharmaceutical composition comprising Zoledronic Acid and a cathepsin K inhibitor for the inhibition of bone metastasis, cancer cell growth or/and inhibition of cancer-therapy-induced bone loss.

6.) A pharmaceutical preparation according to claim 1 or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition of claim 5, in which the cathepsin K inhibitor is selected from the group of N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-ethyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-isopropyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-benzyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-propyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-isopropyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-cyclopentyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-methyl-piperidin-4-yl)-benzamide, and N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(1-propyl-piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-propyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-2,2-dimethyl-3-[4-(4-methyl-piperazin-1-yl)-phenyl]-propionamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-2,2-dimethyl-3-[3-(4-methyl-piperazin-1-yl)-phenyl]-propionamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-ethyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-isopropyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-

ylmethyl]-4-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-piperazin-1-yl-benzamide, 4-(4-{{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-carbamoyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester, 4-(3-{{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-carbamoyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-ethyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-isopropyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(2-dimethylamino-ethoxy)-4-methoxy-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-dimethylaminomethyl-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-ylmethyl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-piperidin-1-yl-ethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(4-ethyl-piperazin-1-yl)-phenyl]-2,2-dimethyl-propionamide or pharmaceutically acceptable salt thereof.

7.) A pharmaceutical preparation according to claim 1 or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition according to claim 5, in which the cat K inhibitor is N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-(1-propyl)-piperazin-1-yl)-benzamide or a pharmaceutically acceptable salt thereof and the bisphosphonate is 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or pharmacologically acceptable salts thereof.